

# Methicillin-Resistant *Staphylococcus aureus*: A Growing Risk in the Hospital and in the Community

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Methicillin-resistant *Staphylococcus aureus* is a common and continuously growing cause of nosocomial and community-acquired infections. The type, disease severity, and clinical outcomes of these infections, as well as the genotypic and susceptibility patterns of the bacteria differ according to the setting in which the infection occurs—a healthcare facility or the community setting. The incidence of these infections in the community setting has been growing consistently in the past decade or so. In addition, resistance to the many current antibiotics used to treat these infections is also growing, further complicating management. Rapid-diagnosis tests and new therapeutic agents are constantly under investigation. The authors review the current understanding of the epidemiology, clinical manifestations, and management of methicillin-resistant *Staphylococcus aureus* infection, including the growing problem of resistance. In addition, they discuss promising diagnostic and therapeutic alternatives, as well as new control strategies to prevent its transmission or the development of infection among carriers. [AHDB. 2009;2(2):86-95.]

Methicillin-resistant *Staphylococcus aureus* (MRSA) refers to isolates that are resistant to  $\beta$ -lactam antibiotics (including penicillins and cephalosporins).<sup>1</sup> According to the Clinical and Laboratory Standards Institute (CLSI), MRSA is defined as isolates with a methicillin minimum inhibitory concentration (MIC)  $\geq 4$   $\mu\text{g/mL}$ ; however, *S aureus* already is considered nonsusceptible to oxacillin if the MIC is  $>2$   $\mu\text{g/mL}$ .<sup>2</sup>

Methicillin resistance is mediated by the penicillin-binding protein (PBP)-2a encoded by the *mecA* gene.  $\beta$ -lactam antibiotics have poor affinity for this altered PBP, and organisms are not killed when exposed to common therapeutic concentrations. The *mecA* gene is located on a mobile genetic element, the staphylococcal chromosome cassette (SCCmec). Sequencing SCCmec from many MRSA strains reveals that there are at least 5 SCCmec types (I-V) that vary in genetic base-pair construction and size.<sup>3</sup>

## Epidemiology

MRSA emerged in England in 1961, 2 years after the

introduction of methicillin, and its incidence has increased steadily since then. In the United States, MRSA was first reported in 1968.

Hospital- or healthcare-associated (HA)-MRSA is different from community-associated (CA)-MRSA in terms of epidemiology, phenotype, and genotype. CA-MRSA is an important pathogen that has become prevalent during the past decade and, according to some reports, is replacing nosocomial MRSA strains. In one study, during a 7-year period, MRSA bloodstream infections caused by CA-MRSA increased from 26% to 49%.<sup>4</sup>

## HA-MRSA

HA-MRSA is associated with severe infections, with high morbidity and mortality rates, such as ventilator-associated and hospital-associated pneumonia, surgical site infections, as well as catheter-related infections.

In the early 1990s, MRSA accounted for 20% to 25% of *S aureus* isolates from hospitalized patients. In 1999, MRSA represented more than 50% of *S aureus* isolates from patients in intensive care units (ICUs) according to the National Nosocomial Infection Surveillance System.<sup>5,6</sup> In 2003, that percentage was approaching 60%. It is now estimated that approximately 70% of all *S aureus* isolated from ICUs are MRSA.<sup>5,6</sup> HA-MRSA carries SCCmec type II and is typified as USA100 or USA200 by pulse-field gel elec-

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**Table 1 Risk Factors for HA-MRSA Infection**

Old age
Previous antibiotic use (particularly cephalosporins and quinolones)
Prolonged hospitalization
Central venous catheter insertion
Ventilator dependency
Hemodialysis
MRSA colonization
Proximity to a patient with MRSA colonization or infection

**Table 2 Risk Factors for CA-MRSA Infection**

Injection drug use
Skin trauma (eg, lacerations, abrasions, tattoos)
Higher body mass index
Cosmetic body shaving
Physical contact with a person who has a draining lesion or is a carrier of MRSA
Incarceration
Military personnel
Previous skin infection with MRSA
Men who have sex with men

trophoresis (PFGE).<sup>7</sup> The major risk factors associated with HA-MRSA are listed in **Table 1**.

### CA-MRSA

In the 1980s, MRSA was isolated among injection drug users who had a history of antibiotic exposure. In 1993, a genetically unique MRSA isolate was reported in Australia among aborigines who had no previous contact with a healthcare system. By the mid-1990s, CA-MRSA infections emerged in New Zealand, the United Kingdom, France, Finland, Canada, Samoa, and the United States.

Initial outbreaks of CA-MRSA in the United States occurred in Native American children in Minnesota, Nebraska, and North Dakota. Later, CA-MRSA infections were identified in other populations, including homosexual men, incarcerated people, athletes, and soldiers. Compared with HA-MRSA, most CA-MRSA cases contain SCCmec type IV or type V, which encode for resistance to methicillin and other  $\beta$ -lactam antibiotics, but generally not for other agents. They are typi-

### KEY POINTS

- ▶ The incidence of MRSA has increased steadily during the past 50 years. Community-associated infection has been on the increase in the past decade and may be replacing nosocomial MRSA strains.
- ▶ Most community-associated MRSA infections are susceptible to doxycycline, minocycline, clindamycin, trimethoprim-sulfamethoxazole, rifampin, and linezolid.
- ▶ Vancomycin has been the drug of choice for hospitalized patients with invasive infections, but emerging treatment failure has been reported.
- ▶ Familiarity with local antibiotic patterns and cultures with susceptibility data are critical for tailoring treatment.
- ▶ In addition to proper drug therapy, basic infection control practices are integral to the prevention and control of hospital-associated MRSA.

fied by a USA300 or USA400 PFGE pattern and frequently carry genes for the cytotoxin Panton-Valentine leukocidin that is associated with the propensity of *S aureus* to cause tissue necrosis.<sup>8</sup>

In 3 US communities, 1647 cases of CA-MRSA infection were reported between 2001 and 2002.<sup>9</sup> Of all MRSA isolates, 8% to 20% were not associated with traditional risk factors and were classified as CA-MRSA.<sup>9</sup> Most caused clinically relevant infections that required treatment; many patients were children and required hospitalization.

CA-MRSA infection often presents as skin and soft-tissue infection (SSTI) in previously healthy individuals. SSTIs may be mild or severe and include pyomyositis or necrotizing fasciitis, osteomyelitis, septic arthritis, Waterhouse-Friderichsen syndrome, pneumonia, and bacteremia.

The risk factors for CA-MRSA, which differ from those of HA-MRSA, are listed in **Table 2**. Transmission of MRSA from colonized pets has also been reported.<sup>10</sup> In many circumstances, a single risk factor could not be identified.

### Pathogenesis

The difference between MRSA and methicillin-sensitive strains is that the former may have acquired a genetic background, which is believed to enhance virulence or the development of more severe and atypical manifestations of the disease.

**Table 3** Important Virulent Factors of *Staphylococcus aureus*

Virulent factor	Role	Clinical consequences
<b>Surface proteins or MSCRAMMs</b>		
Clumping factors	Attachment to blood clots and traumatized tissue	Endocarditis, prosthetic infections
Fibronectin/fibrinogen binding proteins	Attachment to fibronectin/fibrinogen	Septic arthritis, osteomyelitis
Collagen and bone sialoprotein-binding protein	Attachment to collagen, bone	
<b>Invasins</b>		
Proteases, lipases, nucleases, hyaluronidase	Promote bacterial penetration into tissues	Tissue invasion and destruction
Elastase, phospholipase C		
<b>Leukocidal toxins or leucocidins</b>		
Proliferative verrucous leukoplakia, $\delta$ -toxin	Promote host defenses' destruction	Dermonecrosis, necrotizing pneumonia
Protein A	Evade opsonization and phagocytosis	Deep and metastatic infections
Capsular polysaccharides		
Polysaccharide intercellular adhesion	Biofilm production	Persistent infection, specially associated with foreign materials
Accumulation-associated protein		
Biofilm-associated protein		
<b>Exotoxins</b>		
Enterotoxins	Potent gastrointestinal toxins and superantigens that stimulate non-specific T-cell proliferation	Gastroenteritis, food poisoning
Toxic shock syndrome toxin-1	Release several cytokines, specifically tumor necrosis factor and interleukin-1	Toxic shock syndrome
Exfoliative toxin (A & B)	Cleave desmoglein 1, a cadherin that is found in desmosomes in the epidermis	Scalded skin syndrome
MSCRAMMs indicate microbial surface components recognizing adhesive matrix molecules.		

For diseases caused by *S aureus*, the pathogenesis is considered to be multifactorial. Progress in molecular biology techniques has allowed identification of many virulence factors (specific genes have been cloned and sequenced, and protein toxins purified); however, it is difficult to determine precisely the role of many of them.

Staphylococcal infections occur frequently but usually remain localized at the portal of entry by normal host defenses. MRSA colonization is an important risk factor for the development of infection. It is estimated that 20% to 30% of individuals carry *S aureus* in their nares and in other areas, such as the axillae, groin, or gastrointestinal tract. When the host barriers are broken, "commensal" *S aureus* may invade deeper structures and produce subsequent infection. Another por-

tal of entry is the respiratory tract. Staphylococcal pneumonia is a severe condition affecting young, previously healthy individuals during or after influenza.<sup>11</sup> **Table 3** summarizes the most important virulence factors and their roles in the disease.

### CA-MRSA Clinical Syndromes

Almost 80% of CA-MRSA infections in the United States are SSTIs. Abscess and cellulitis are the most common, and 60% of SSTIs seen in emergency departments are produced by MRSA. The median age for CA-MRSA infection in adults ranges from 20 to 47 years, and SSTIs are more frequent among nonwhite men. The majority of CA-MRSA infections, particularly those involving the skin and soft structures, are

not severe and are considered to have a low mortality rate (as compared with infections caused by nosocomial MRSA strains); however, severe and life-threatening episodes of invasive CA-MRSA infections have been reported with increased frequency worldwide.<sup>12</sup>

Less common, but severe forms of disease caused by CA-MRSA are:

- **Necrotizing fasciitis**, a life-threatening infection that requires urgent surgical and medical therapy; associated conditions or risk factors include previous MRSA infection, hepatitis C, diabetes mellitus, current or past injection drug use, cancer, and HIV infection
- **Pyomyositis**, initially considered a tropical disease, is now recognized in areas of temperate climates and especially in patients with HIV and intravenous drug users
- **Necrotizing community-acquired pneumonia (CAP)** is associated with influenza, and generally occurs in previously healthy young individuals. During the 2003-2004 influenza season, 15 cases of MRSA-CAP, with 4 deaths (fatality rate 26.7%), were reported from 9 states.<sup>13</sup> In January 2007, the Centers for Disease Control and Prevention (CDC) received reports of 10 cases of severe MRSA-CAP, including 6 deaths, among previously healthy persons in Louisiana and Georgia<sup>14</sup>
- **Infective endocarditis** is a common and often devastating complication of *S aureus* bacteremia<sup>15</sup>; risk factors include prosthetic valve, underlying valvular defects, injection drug use, intravascular catheter infection, and persistent bacteremia
- **Septic arthritis and osteomyelitis** may be caused by direct injury or as a complication of *S aureus* bacteremia
- **Sepsis** (with or without Waterhouse-Friderichsen syndrome). Waterhouse-Friderichsen syndrome is characterized by petechial rash, coagulopathy, cardiovascular collapse, and bilateral adrenal hemorrhage. It generally is associated with fulminant meningococcemia; however, 3 fatal cases produced by *S aureus* were reported in 2005 in children, 2 of which were caused by CA-MRSA.<sup>16</sup>

### HA-MRSA Clinical Syndromes

HA-MRSA infections are associated with prolonged hospital stay, increased mortality, and increased costs. In 2003, 64.4% of *S aureus* infections in ICUs were associated with methicillin-resistant strains.<sup>5,6</sup> MRSA is a suspected pathogen in nearly all types of hospital infections.

The most common manifestations of HA-MRSA infections are:

- Surgical wound skin and skin structure infection (SSSI)
- Osteomyelitis and septic arthritis as complications of orthopedic surgery, including prosthetic device infections
- Bacteremia
- Healthcare- and ventilator-associated pneumonia.

### Treatment of MRSA Infection

#### Outpatient Drug Therapy

Uncomplicated SSTIs (ie, those without associated sepsis or hemodynamic instability) can be managed with incision and drainage if an abscess is present. Topical antimicrobial therapy sometimes is used to treat limited and superficial MRSA skin infections (eg, impetigo). The most known agents are bacitracin (alone or in combination with polymyxin and neomycin), mupirocin, and retapamulin. Emerging resistance to mupirocin is now being reported worldwide, particularly in healthcare facilities where it is used extensively to prevent infection and transmission from carriers.

The drug of choice for the ambulatory setting has not been clearly established. Most CA-MRSA are susceptible to doxycycline, minocycline, clindamycin, trimethoprim-sulfamethoxazole (TMP-SMX), chloramphenicol, rifampin, and linezolid. Familiarity with local antibiotic patterns and cultures with susceptibility data are critical for tailoring treatment. **Table 4** lists oral agents available for the treatment of CA-MRSA.

Susceptibility to erythromycin ranges from 5% to 64% in different geographic areas.<sup>11</sup> Clindamycin has good activity against MRSA and is capable of inhibiting bacterial toxin production. Awareness of local clindamycin resistance rates is important. Some experts recommend avoiding use of this antibiotic empirically if the local rate of resistance is 10% to 15%. In addition, isolates that appear susceptible to clindamycin but are resistant to erythromycin by standard susceptibility testing may be capable of inducing resistance to clindamycin. The double disk-diffusion test detects isolates that may become resistant to clindamycin during treatment.

TMP-SMX and tetracyclines are generally not recommended as sole empirical therapy in the treatment of nonpurulent cellulitis, because group A streptococci, which are usually resistant to these antibiotics, may be involved in coinfection. Resistance of group A streptococci to tetracyclines has been well documented, whereas resistance to TMP-SMX remains poorly known.<sup>8</sup> Some physicians add an active  $\beta$ -lactam antibiotic to cover streptococci.

Few data exist on the efficacy of the long-acting tetracyclines (doxycycline and minocycline) against MRSA

**Table 4** Oral Agents Used for the Treatment of MRSA in the Community Setting

Medication	Usual dose (adults)	Main side effects/comments	Cost, \$
Clindamycin (Cleocin)	300 mg 3 times daily	<i>Clostridium difficile</i> diarrhea Many patients dislike taste of suspension	6.62 (300 mg)
Trimethoprim-sulfamethoxazole (Bactrim, Septra)	1-2 double strength tablet twice daily (tablet: 160/800 mg)	Nausea, vomiting, rash, photosensitivity, hematologic suppression (especially thrombocytopenia) No adequate controlled trials to prove efficacy	1.15 (160/800 mg)
<i>Tetracyclines</i> Doxycycline (Doryx, Monodox, Vibramycin, Vibra-Tabs)	100-200 mg/d, 1 or 2 divided doses	Nausea, photosensitivity	0.08-0.11 (100 mg)
Minocycline (Dynacin, Minocin, Myrac)	200 mg/d, in 2 divided doses	Nausea, photosensitivity	3.40 (100 mg)
Linezolid (Zyvox)	600 mg twice daily	Myelosuppression (especially thrombocytopenia, can also cause anemia, neutropenia), mostly with prolonged use Cost is relatively high	65.00 (600 mg)
Rifampin (Rifadin, Rimactane)	20 mg/kg daily 1 or 2 divided doses; max: 600 mg/d	Discoloration of body fluids, liver function abnormalities, drug interactions Resistance mutation emergence if used alone	1.58 (150 mg) 2.24 (300 mg)

Cost source: Average wholesale price from Red Book, 2008. Evanston, IL: Thomson Healthcare; 2008.

infection. In one retrospective case series of 24 patients with serious tetracycline-susceptible MRSA infections, clinical cure was achieved in 83% of patients.<sup>17</sup>

Linezolid is active against almost all isolates of CA-MRSA and streptococci; however, it should be reserved for patients who do not respond or cannot tolerate traditional agents. The disadvantages of using linezolid include cost, hematologic side effects, and the potential to induce resistance among *S aureus* strains.<sup>18</sup>

Rifampin has excellent activity against MRSA. It has been used with good results in combination with tetracycline or with TMP-SMX, although solid data are not available to support this approach. Rifampin monotherapy is contraindicated due to the rapid emergence of resistant mutants.

Fluoroquinolones should not be used to treat SSTIs caused by MRSA; resistance to ciprofloxacin develops rapidly during therapy and widespread resistance is prevalent in many regions.

### Parenteral Therapy

Parenteral therapy (Table 5) should be considered for patients with severe SSTIs, fever, or with other signs of systemic illness, and patients with diabetes, immunosuppression, or other significant comorbid conditions.

Vancomycin has been the drug of choice for hospi-

talized patients with invasive MRSA infections. Nevertheless serious problems with vancomycin have been identified. Recent studies have shown emergence of treatment failures in correlation with increasing, but still considered within the “susceptible” range, vancomycin MICs (<0.5 vs 2.0 µg/mL).<sup>19,20</sup> Because of the results of those studies, the CLSI changed the susceptibility and resistance breakpoints from ≤4 µg/mL to ≤2 µg/mL for “susceptible” and from 8 µg/mL to 16 µg/mL to 4 µg/mL to 8 µg/mL for “intermediate” resistance.<sup>2</sup>

A significant concern remains for patients infected with MRSA who have MICs at the upper range of the susceptible zone—the trough levels of vancomycin (15 µg/mL-20 µg/mL) required to treat such patients may result in renal toxicity. In addition, treatment failure has been attributed to vancomycin intermediate-resistant *S aureus*.<sup>19</sup> Failure due to strains that exhibit heterogeneous resistance to vancomycin also occurs.<sup>19</sup> These strains are missed by routine laboratory methodologies.

Vancomycin-resistant *S aureus* (VRSA) is now a threatening reality. A total of 7 cases were identified in the United States between 2002 and 2006; 5 in Michigan, 1 in Pennsylvania, and 1 in New York.<sup>20</sup> All VRSA isolates carried the *vanA* gene and had a median vancomycin MIC of 512 µg/mL.<sup>20</sup> For patients who fail



**Table 5** Intravenous Agents for the Treatment of MRSA in the Hospital Setting

Medication	Usual dose (adults)	Side effects/comments	Cost, \$
Vancomycin (Vancocin)	1 g every 12 h	Not as effective as $\beta$ -lactam agents for MRSA Treatment failure reported with MRSA strains High MIC potentiates renal toxicity at high trough levels (ie, 15 g/mL-20 g/mL)	7.75 (1 g)
Linezolid (Zyvox)	600 mg every 12 h	Reversible myelosuppression, usually after 2 weeks of therapy; lactic acidosis, peripheral/optic neuropathy; serotonin syndrome Good tissue penetration, particularly in the epithelial-lining tissue	82.00 (600 mg)
Daptomycin (Cubicin)	SSTIs: 4 mg/kg daily Bacteremia/IE: 6 mg/kg daily	Potential muscle toxicity Recommended not to be used with statins Not recommended for pneumonia	206.00 (500 mg)
Tigecycline (Tygacil)	100 mg/d initially, then 50 mg every 12 h	High incidence of nausea, vomiting (>20%) Pregnancy category D Do not use in children <18 years	57.00 (50 mg)
Ceftobiprole (pending approval)	0.5 g every 12 h for gram-positive infections (including MRSA)	Nausea (14%), taste disturbance (8%), vomiting (7%) For treatment of cSSSIs, including diabetic foot infections	N/A
Clindamycin (Cleocin)	600-900 mg every 8 h	May be given in regions with low likelihood of resistance Major cause of <i>Clostridium difficile</i> diarrhea	10.51 (600 mg)
Quinupristin + dalbapristin (Synercid)	7.5 mg/kg every 8 h	Venous irritation (5%) with peripheral line use, asymptomatic indirect; hyperbilirubinemia; arthralgia	150.00 (350/150 mg)

Cost source: Average wholesale price from Red Book, 2008. Evanston, IL: Thomson Healthcare; 2008.

cSSSIs indicates complicated skin and skin structure infections; IE, infective endocarditis; MIC, minimum inhibitory concentration; SSTIs, skin and soft-tissue infections.

to respond or cannot tolerate vancomycin, the optimal alternative parenteral agent is not known.

Linezolid, daptomycin, tigecycline, and quinupristin-dalbapristin are indicated for the treatment of SSTIs. Among this group, only daptomycin also has an indication for bacteremia and endocarditis.

Among the older agents, treatment data for MRSA are limited. Parenteral clindamycin may be given in regions where the likelihood of resistance is low, but this agent is considered bacteriostatic and may not be an effective choice for deep-seated infections. In a 1992 study, investigators compared parenteral TMP-SMX with vancomycin for the treatment of invasive *S aureus* infections in intravenous drug users (43 patients received TMP-SMX and 58 received vancomycin).<sup>21</sup> TMP-SMX proved to be inferior to vancomycin only in cases of methicillin-sensitive *S aureus* infections. TMP-SMX was successful in treating all MRSA infections, including tricuspid-valve endocarditis. The authors concluded that TMP-SMX could be

considered as an alternative to vancomycin in selected cases of MRSA infection.<sup>21</sup>

Teicoplanin is another glycopeptide with similar efficacy to vancomycin, but with less toxicity; however, it is not available in the United States.

Daptomycin is a cyclic lipopeptide, with rapid bactericidal activity against MRSA produced by depolarization of the bacterial cell membrane. This drug has been approved by the US Food and Drug Administration (FDA) for the treatment of complicated SSTIs at a daily dose of 4 mg/kg, and at a daily dose of 6 mg/kg for the management of bacteremia and right-sided endocarditis. In a randomized trial that included 45 patients with complicated SSTIs caused by MRSA, daptomycin had similar efficacy to vancomycin, with a clinical success rate of 83%.<sup>22</sup> In another randomized trial in patients with *S aureus* bacteremia with or without right-sided endocarditis, daptomycin monotherapy was not inferior to vancomycin plus gentamicin; 53 of 120 patients had a

successful outcome with daptomycin compared with 48 of 115 patients who received vancomycin (99 of whom had MRSA infections).<sup>23</sup> Daptomycin should not be used to treat pneumonia, because its activity is inhibited by pulmonary surfactant.

Linezolid is an alternative agent to glycopeptides. It inhibits the initiation of protein synthesis at the 50S ribosome. Although bacteriostatic for MRSA, it has excellent bioavailability and tissue penetration, particularly in the epithelial lining fluid of the lungs, making this antibiotic a potentially useful option in cases of MRSA pneumonia.

Tigecycline, a parenteral glycylcycline-minocycline derivative, was approved by the FDA in 2005 for the treatment of complicated SSTIs, including those infected with MRSA. A study that combined data from 2 clinical trials demonstrated tigecycline to be as effective as the combination of vancomycin and aztreonam for the management of complicated SSTIs. For MRSA infections, the cure rate was 78.4% for tigecycline compared with 76.5% for vancomycin plus aztreonam.<sup>24</sup>

### Investigational Antimicrobials

Several new agents are currently under development—dalbavancin, telavancin, and oritavancin are semisynthetic glycopeptides characterized by prolonged plasma half-lives. Dalbavancin is bactericidal against gram-positive cocci, including MRSA, and its estimated half-life of 6 to 12 days permits once-weekly dosing.

Clinical trials evaluating the efficacy of dalbavancin demonstrated that it is not inferior to vancomycin in the treatment of catheter-related infection caused by gram-positive pathogens (including MRSA). The success rate for dalbavancin was 87% versus 50% for vancomycin.<sup>25</sup> Dalbavancin was also as effective as linezolid for the treatment of complicated SSTIs, with a success rate of 91% compared with 89% for linezolid in patients with MRSA infections.<sup>26</sup>

Ceftobiprole is an advanced-generation pyrolidinone cephalosporin with capacity to bind to PBP-2a. The results of 2 multicenter noninferiority trials involving approximately 1600 patients with complicated SSSIs (cSSSIs) were reported recently. The first trial included patients with gram-positive cSSSI; cure rates were 93.3% and 93.5% for ceftobiprole treatment and vancomycin treatment, respectively. The second trial included a broad range of cSSSIs; clinical cure rate among patients with MRSA infections who received ceftobiprole was 91.4% compared with 86.1% for vancomycin plus ceftazidime.<sup>27</sup>

Ceftaroline, another new broad-spectrum cephalos-

porin, is currently under investigation (in phase 2 and 3 clinical trials) in patients with *S aureus* cSSSIs.

### Immunointervention

Pooled staphylococcal antibody preparations that neutralize staphylococcal superantigen toxins are being prepared for the treatment of toxic shock syndrome. Telfibazumab is a humanized monoclonal antibody directed at microbial surface compounds recognizing adhesive matrix molecule clumping factor A, a protein on the *S aureus* surface that binds to human fibrinogen. This drug is being investigated for the treatment of *S aureus* infections and also for potential prevention of disease.<sup>28</sup>

StaphVAX, a promising *S aureus* polysaccharide conjugate vaccine, has been demonstrated to offer protection against *S aureus* bacteremia in dialysis patients. However, the effect is temporary, requiring a booster dose every 6 months.<sup>29</sup> In a recent (yet to be published) phase 3, confirmatory study involving more than 3500 hemodialysis patients, StaphVAX did not offer any more benefit than placebo, and therefore, its development has been halted.<sup>30</sup>

### New Test for Rapid Diagnosis of *S aureus* Bacteremia

Based on a fluorescent in-situ hybridization (FISH) assay with peptide nucleic-acid (PNA) probes that target specific sequences of *S aureus* 16S rRNA, the new PNA FISH test allows for rapid diagnosis of *S aureus* bacteremia. The performance of the PNA FISH assay was evaluated using 285 blood cultures that had gram-positive cocci resembling staphylococci on Gram's stain. The sensitivity, specificity, and positive and negative predictive values of the PNA FISH test for the rapid identification of *S aureus* directly from positive blood culture bottles were 100%, 99.4%, 99.2%, and 100%, respectively. Results are available within 3 hours after blood cultures turn positive.<sup>31</sup>

The impact of the rapid differentiation of *S aureus* from coagulase-negative staphylococci in blood cultures using PNA FISH was evaluated in a recent retrospective, cost-effective analysis.<sup>32</sup> When comparing the PNA FISH assay results with those for a control group (53 and 34 patients, respectively), a significant reduction was found with use of the new assay in median length of hospital stay from 6 to 4 days, as well as a trend toward reduced vancomycin use, with a decreased cost of \$4000 per patient.<sup>32</sup>

### Continued Emergence of Resistance in *S aureus*

*S aureus* has developed resistance to most antibiotics, including penicillin, methicillin, linezolid, and daptomycin.

mycin, rather rapidly. Resistant strains were reported from around the world, within 1 or 2 years after the introduction of each of these agents. With vancomycin, the history was different; after the introduction of vancomycin in 1958, the first vancomycin intermediate-resistant *S aureus* was found in 1997 in Japan (39 years later). The first truly resistant isolate (ie, VRSA) was identified in Detroit, Michigan, in 2002. According to the CLSI, vancomycin intermediate-resistant *S aureus* (or glycopeptide intermediate-resistant *S aureus*) and VRSA are defined as having MICs of 4 µg/mL to 8 µg/mL, and ≥16 µg/mL, respectively.<sup>2</sup>

In VRSA strains, resistance is mediated by the presence of operons that encode enzymes that eliminate precursors with high affinity to vancomycin. In glycopeptide intermediate-resistant *S aureus* strains, reduced susceptibility is the result of the production of increased numbers of D-Ala-D-Ala residues on the nascent cell wall that serve as dead-end binding sites for vancomycin. The result is a reduced vancomycin diffusion coefficient and sequestration of this drug within the cell wall by these false targets.<sup>33</sup>

A microbiological definition of daptomycin resistance has not been established yet; however, a value of MIC >1.0 µg/mL is considered nonsusceptible in accordance with the CLSI guidelines.<sup>2</sup>

Wild-type *S aureus* with MICs of >1.0 µg/mL are rare but have been recovered from patients who had previously received either vancomycin, daptomycin, or, in some cases, had not received antibiotics previously. At this time, multiple studies have reported that 90% of *S aureus* isolates in healthcare settings still have daptomycin MICs <0.5 µg/mL.<sup>34</sup> It is thought that glycopeptide exposure induces the formation of a thicker cell wall, thus preventing the diffusion of daptomycin into the bacteria. In addition, mutations in certain genes, such as *MPRF* (which encodes lysylphosphatidylglycerol synthetase), *YYCG* (which encodes sensor histidine kinase), and *RPOB/RPOC* (encode β and β' subunits of RNA polymerase), were found in *S aureus* strains with daptomycin MIC of more than 1.0 µg/mL.<sup>35</sup>

Linezolid resistance is associated with mutations in the central loop of domain V in the 23S ribosomal RNA, and increased MICs are associated with greater numbers of mutations. The most frequent mutation associated with linezolid resistance in both staphylococci and enterococci strains is G2576T. Another mutation (T2500A) was characterized in a single patient isolate of MRSA. Recently, the presence of the *CFR* gene (a gene encoding an rRNA methyltransferase, and is called *CFR* for chloramphenicol-florfenicol resistance) has been

identified in a clinical MRSA isolate (designated CM-05) from Colombia.<sup>33,36</sup> Linezolid resistance in MRSA is still considered rare.

### Controlling MRSA Infection

Optimal measures for the prevention of MRSA infections remain under investigation. The most common source of HA-MRSA is colonized or infected patients; the most important mode of transmission is via hands, especially from healthcare personnel. Basic infection control practices are integral to the prevention and control of MRSA in healthcare settings. In its "Information about MRSA for Healthcare Personnel" and the *Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings 2007*, the CDC emphasizes several standard and contact precautions to prevent the transmission of MRSA.<sup>37</sup>

### Community-associated infections can recur in individuals and can spread within families.

Community-associated infections can recur in individuals and can spread within families. Clinicians should educate patients or their caretakers, and when possible, household members, on methods to limit further spread of infection. The CDC has recommended the following measures in an effort to prevent the spread of CA-MRSA infections in the community<sup>37</sup>:

- Keep hands clean by washing thoroughly with soap and water or by using an alcohol-based hand sanitizer
- Keep cuts and scrapes clean and covered with a bandage until healed
- Avoid contact with other people's wounds or bandages
- Avoid sharing personal items, such as towels, washcloths, razors, clothing, or uniforms.

To date, no data support the use of agents to eliminate colonization in patients with MRSA infection or their contacts. However, it may be reasonable to attempt decolonization if a patient has had multiple recurrences of MRSA infection or ongoing MRSA transmission is occurring in a well-defined, closely associated cohort (such as a household).<sup>38</sup>

The role of early screening for MRSA colonization in hospitalized patients is unclear. In a recent study involving more than 21,000 surgical patients, 2 MRSA control strategies (rapid screening on admission plus standard infection control measures vs standard infection control alone) were used to determine the effect of an early MRSA detection strategy on nosocomial



MRSA infection rates. Rapid MRSA screening on admission did not reduce the rate of nosocomial MRSA infection.<sup>39</sup>

## Conclusion

MRSA now represents a common infectious agent in any environment. More virulent than ever, MRSA keeps producing high rates of morbidity and mortality. MRSA also has the ability to become easily resistant every time a new therapeutic agent is introduced, except for vancomycin, which was considered useful for the past 40 years; however, increasing rates of treatment failure with strains reported to have MICs in the “susceptible” range have been widely documented. The continuous emergence of resistant strains has created an enormous difficulty for the management of MRSA infections. It is now crucial to make the diagnosis very early and in an effective way. Many potent antibiotics are being developed as well as promising vaccines; however, control measures to identify populations at risk and strategies to prevent transmission should play an essential aspect of care. ■

## Disclosure Statement

Dr Levine is on the Speakers' Bureau of Cubist Pharmaceuticals and Novartis; receives research support from Cubist and Theravance Therapeutics (Astellas); and is on the advisory board of Cubist, Merck & Co, Novartis, and Theravance.

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## STAKEHOLDER PERSPECTIVE

### Prevention and Control of Methicillin-Resistant *Staphylococcus aureus*

**MEDICAL/PHARMACY DIRECTORS:** The medical and operational complexities of responding to antimicrobial resistance, convincingly demonstrated by the nearly 50 years of human experience with methicillin-resistant *Staphylococcus aureus* (MRSA), are well described in this expansive review.

Formerly encountered only in tertiary care or long-term care settings, MRSA has become a significant infection control challenge in nearly all healthcare settings. The boundaries surrounding healthcare-associated (HA)-MRSA infections have rapidly dissolved with the recent evolution of strains that cause disease in persons within the community. These new community-associated (CA)-MRSA strains have unique virulence factors that may facilitate the transmission of the microbe and the development of disease. Outbreaks of infection have occurred in group settings in the community, such as prisons, schools, military barracks, and households.

The cost of treating hospitalized patients with HA-MRSA infections is nearly double that of treating hospitalized patients without these infections, and the cost for treating CA-MRSA infections exceeds the cost of treating infections with methicillin-sensitive strains. These increased costs pose formidable challenges for health plans and insurers, and represent a growing burden on the US healthcare industry as a whole.

Antimicrobial treatment for MRSA is complex, dynamic, and subject to localized pressures, thereby requiring constant attention by pharmacy and formulary decision makers. The continuing emergence of additional resistance capacity as we use new drugs is especially troublesome and mandates adher-

ence to standards of judicious use of current antimicrobial therapies.

Recent advances have increased the number of new and promising antimicrobials in our armamentarium pipeline. Ensuring that effective therapies successfully reach use in practice is as difficult now as it always has been. Attempts to develop effective vaccines against virulence factors of *S aureus* have had mixed results, and no new vaccine appears ready for use yet.

In the face of these complex medical challenges, nonpharmaceutical approaches, specifically, proven infection control measures, may represent our best chance to control the spread of MRSA in both the healthcare and community settings. Educating healthcare workers and family members in the basics of hand washing may represent the greatest weapon against drug-resistant microbes.

Addressing the many issues of multidrug-resistant organisms, such as MRSA, requires a long-term commitment from physicians, pharmacists, health plan directors, epidemiologists, and benefits designers. Policies and procedures for antimicrobial use and payer coverage must always consider the current local resistance patterns. Only when our response is coordinated and inclusive will we tip the balance against MRSA and for our patients.

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